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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,586	06/19/2001	Yann Echelard	10275-120001 / GTC-31 US	2580

26161 7590 01/14/2003

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	15

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,586	ECHELARD ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *10,13 and 16-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-12 and 14-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-31 are pending in the present application.

Applicants' election with traverse the invention of Group I (claims 1-9, 11-12 and 14-15) in Paper No. 14 is acknowledged.

Applicants traverse mainly the restriction of claims 10, 13 and 16 from Group I because Applicants argue that the only difference between claim 9 of Group I and claim 10 of Group II is that claim 9 recites that the cell is an oocyte, namely microinjection type techniques, whereas claim 10 recites that the cell is a somatic cell, and then the somatic cell or its nucleus is introduced into an oocyte, namely nuclear transfer techniques, and that these techniques were known at the time of filing and do not lead to the claims being patentably distinct from each other. Accordingly, Applicants believe that the restriction is improper. Applicants' arguments are respectfully found to be unpersuasive because the methods of producing a transgenic mammal capable of expressing an active PDGF molecule in its milk via conventional microinjection type techniques or via nuclear transfer techniques are distinct methods involving different method steps and starting materials, as well as different technical considerations for attaining the desired results (for this instance a transgenic mammal capable of expressing an active PDGF molecule in its milk). Furthermore, these methods can be carried out independently one from the other. Accordingly, the claims are properly restricted. This Restriction is made FINAL.

Claims 10, 13 and 16-31 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 1-9, 11-12 and 14-15 are examined on the merits herein.

Claim Objections

Claims 1, 7-8, 11 and 14 are objected to because of the following informalities: As defined by the present application the term "mammal" excludes human (see page 15, lines 10-11), however this definition is not consistent with the commonly accepting meaning of the term "mammal". Since Applicants intend to exclude humans from the term "mammal" used in the present application, then Applicants should use the phrase - - non-human mammal - - to reflect such intention. Appropriate correction is required.

Claim 8 is objected to because of the following infirmity: the phrase "a PDGF chains" is grammatically incorrect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-9, 11-12 and 14-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method of producing a non-human transgenic mammal capable of expressing an active PDGF molecule in its milk, comprising: introducing into a fertilized egg a nucleic acid sequence encoding a PDGF chain operably linked to a promoter which directs expression in mammary epithelial cells; and allowing the fertilized egg to

give rise to a non-human transgenic mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk is in active form;

(2) A method of producing a non-human transgenic mammal capable of expressing an active PDGF molecule in its milk, comprising: (a) introducing into a fertilized egg a nucleic acid sequence encoding a PDGF-A chain operably linked to a promoter which directs expression in mammary epithelial cells; (b) introducing into the fertilized egg of step (a) a nucleic acid sequence encoding a PDGF-B chain operably linked to a promoter which directs expression in mammary epithelial cells; and (c) allowing the fertilized egg of step (b) to give rise to a non-human transgenic mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk is in active form;

(3) A method of producing a non-human transgenic mammal capable of expressing an active PDGF molecule in its milk, comprising: (a) providing a fertilized egg from a non-human transgenic mammal whose germ and somatic cells comprise a nucleic acid sequence encoding a PDGF-A chain operably linked to a promoter which directs expression in mammary epithelial cells; (b) introducing into the fertilized egg a nucleic acid sequence encoding a PDGF-B chain operably linked to a promoter which directs expression in mammary epithelial cells; and (c) allowing the fertilized egg of step (c) to give rise to a non-human transgenic mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk is in active form;

does not reasonably provide enablement for methods of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk by introducing a nucleic acid sequence encoding PDGF into a cell of any other type and allowing the cell to give rise to the transgenic mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 8-9 and 11-12 are directed to methods of producing a transgenic mammal capable of expressing an active PDGF molecule in its milk, comprising introducing into a cell a nucleic acid sequence encoding a PDGF chain operably linked to a promoter which directs expression in mammary epithelial cells; and allowing the cell to give rise to a transgenic mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk is in active form; the same methods wherein the cell is an oocyte.

Claims 14-15 are drawn to a method of producing a transgenic mammal capable of expressing an active PDGF molecule in its milk, comprising providing a cell from a transgenic mammal whose germ and somatic cells comprise a nucleic acid sequenc

encoding a PDGF-A chain operably linked to a promoter which directs expression in mammary epeithelial cells; and introducing into the cell a nucleic acid sequence encoding a PDGF-B chain operably linked to a promoter which directs expression in mammary epithelial cells; and allowing the cell to give rise to a transgenic mammal, wherein the transgenic mammal expresses PDGF in its milk and at least 30% of the PDGF is present in the milk is in active form; the same method wherein the cell is an oocyte.

The specification teaches by exemplification showing the construction of expression vectors BC701 and BC734 which comprises a nucleic acid sequence encoding a PDGF-B chain and a bicistronic nucleic acid sequence encoding both a PDGF-A chain and a PDGF-B chain, respectively. The isolated BC701 expression cassette is microinjected into fertilized eggs of mice, and BC701 transgenic mouse lines are established. Applicants further disclose that PDGF-B is expressed at a level of approximately 2-4 mg/ml in the milk of the founder transgenic female 647 and to a level of 0.5-1.0 mg/ml in the milk of the founder transgenic female 484.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention which is drawn to methods of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk by introducing into any cell a nucleic acid sequence encoding a PDGF chain operably linked to a promoter which directs expression in mammary epithelial cell and allowing said cell to give rise to a transgenic mammal, for the following reasons.

(1) The state of the prior art. With respect to the elected invention, at the effective filing date of the present application, apart from the introduction of a DNA sequence encoding a heterologous protein into a fertilized egg via microinjection to generate a transgenic non-human mammal expressing a heterologous protein in the mammal's milk as evidenced by the teachings of Houdebine et al. (U.S. Patent No. 5,965,788; see col. 2, lines 57-61), neither the prior art nor the instant specification provide any guidance for a skilled artisan on how to make and use of any cell other than a fertilized egg to generate a non-human transgenic mammal expressing an active PDGF molecule in its milk via the conventional microinjection techniques.

(2) The amount of direction or guidance provided and the unpredictability of the art. Apart from the exemplification showing that the isolated BC701 expression cassette was microinjected into fertilized eggs of mice, and BC701 transgenic mouse lines were generated and established; the instant specification fails to provide sufficient guidance for a skilled artisan on how to use cells other than a fertilized egg containing the heterologous expression cassette to give rise a non-human transgenic mammal with the desired properties (e.g., expressing PDGF molecule in its milk and at least 30% of the PDGF is present in the milk in its active form). Furthermore, it should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

(3) The absence of a working example. The instant specification fails to provide any working example on using any cell other than a fertilized egg containing a heterologous expression cassette to generate a non-human transgenic mammal with the desired properties.

(4) The breadth of the claims. As written, the claims encompass the use of any cell to generate the desired non-human transgenic mammal as long as the cell contains a nucleic acid encoding a PDGF chain operably linked to a promoter which directs expression in mammary epithelial cells. However, the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use the full scope of the methods as claimed.

As set forth in *In re* Fisher, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11-12 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houdebine et al. (U.S. Patent No. 5,965,788) in view of Eichner et al. (U.S. Patent No. 5,665,567; IDS) and Hart et al. (Science 240:1529-1521, 1988; IDS).

Houbedine et al. teach a method of producing a transgenic non-human mammal whose genome comprises a DNA construct comprising a rabbit WAP promoter directing the expression of a DNA sequence encoding a heterologous protein. Houbedine et al. also teach methods of using the transgenic non-human mammal in the production of recoverable amounts of a heterologous protein in the mammal's milk, and that the mammal is a bioreactor for a protein of interest (see abstract and the claims). Houdebine et al. listed different heterologous proteins to be expressed such as growth factors, interleukins, stimulating factors, kinases, coagulation factors among others (see col. 4), and various promoters (e.g., alpha-casein, beta-casein, beta-lactoglobulin, WAP) that have been used to make transgenic non-human mammals expressing heterologous protein in their milk (see Table 1). Houdebine et al. also teach that the

DNA constructs are introduced by microinjection into fertilized eggs at the one cell up to the 8-cell stage in the making of the transgenic non-human mammals (see col. 2, lines 57-61).

Houdebine et al. do not specifically teach a method of producing a transgenic non-human mammal capable of expressing an active PDGF molecule in its milk or a method of producing PDGF using the same.

However, at the effective filing date of the present application, Eichner et al. teach that cDNA clones encoding for the PDGF-A chain and PDGF-B chains are available and that different routes for preparing recombinant PDGF homodimers are known (see col. 3, lines 32-53; col. 4, lines 34-38). Additionally, recombinant PDGF-AB heterodimers have been prepared in eukaryotic expression systems wherein both PDGF-A and PDGF-B genes are located on one vector in independent transcription units (col. 4, lines 48-59). Eichner et al. further teach that it is known in the literature that when both PDGF genes are expressed in a eukaryotic cell, 30% or more of the produced PDGF is in the form of a homodimer (col. 5, lines 5-9). Moreover, Eichner et al. disclose the use of a biscistronic expression vector system in which an IRES sequence is located between the first and second cistrons and in which the PDGF-B chain coding gene is located in the first cistron to produce predominantly recombinant PDGF-AB heterodimers (see abstract and the claims). The PDGF-species are involved in the wound healing process, and the most frequent isoform PDGF-AB has been taught by Eichner et al. to be formulated in a pharmaceutical preparation for wound healing, for

skin regeneration, skin smoothening, for preventing of scaring or of skin ageing or for sunburn (see col. 3, line 64 continues to line 2 of col. 4; col. 7, lines 46-62).

At the effective filing date of the present application, Hart et al. also teach that there are two populations of PDGF receptor that differ in ligand-binding specificity for the PDGF species. It is reported that the B receptor binds only the PDGF-BB dimmers whereas the A/B receptor binds PDGF-AA, PDGF-BB and PDGF-AB dimmers and that human dermal fibroblasts appear to express seven times as much as B receptor as A/B receptor (see abstract). Other cell types have been noted to have different ratio for the two classes of PDGF receptor (page 1531, col. 1, bottom of the first full paragraph).

Accordingly, it would have been obvious and within the scope of a skilled artisan to modify the methods taught by Houdebine et al. by introducing a nucleic acid sequence encoding a PDGF-A chain and/or a PDGF-B chain either in separate nucleic acid molecules or in a biscistronic expression vector into a fertilized egg, wherein the nucleic acid sequence is operatively linked to a promoter which directs the expression of a PDGF into mammary gland epithelial cells, in light of the teachings of Eichner et al. to produce a non-human transgenic mammal capable of expressing a PDGF molecule in its milk, and for preparing transgenically produced PDGF using the same.

One of ordinary skilled artisan would have been motivated to carry out the above modification because the mitogenic PDGF-species are involved in the wound healing process, and the most frequent isoform PDGF-AB has been taught by Eichner et al. to be formulated in a pharmaceutical preparation for wound healing, for skin regeneration, skin smoothening, for preventing of scaring or of skin ageing or for sunburn (see col. 3,

line 64 continues to line 2 of col. 4; col. 7, lines 46-62). Furthermore, Houdebine et al. already teach that the production of a recombinant protein secreted in the milk of a non-human transgenic mammal provides a highly desirable system for obtaining the recombinant protein in large quantities, in mature state due to proper glycosylation, phosphorylation and enzymatic processing, as well as the relative ease of collecting and recovering the recombinant protein in milk (see col. 1, lines 30-41).

With respect to claims 14-15, it would also have been obvious and within the scope of skill for an ordinary skilled artisan to introduce into a fertilized egg obtained from a non-human transgenic mammal whose germ cell and somatic cells already containing a nucleic acid sequence encoding a PDGF-A chain operably linked to a promoter which directs expression in mammary epithelial cells with a nucleic acid sequence encoding a PDGF-B chain operably linked to a promoter which directs expression in mammary epithelial cells in light of the teachings of Hart et al. One of ordinary skilled artisan would have been motivated to carry out the above modification to obtain different ratios of PDGF species in the transgenically produced milk that would produce different effects on different treated cell types depending on their differentially expressed B and A/B receptors. This is because Hart et al. already teach that the B receptor binds only the PDGF-BB dimmers whereas the A/B receptor binds PDGF-AA, PDGF-BB and PDGF-AB dimmers and that human dermal fibroblasts and other cell types appear to express different ratios of the two classes B receptor as A/B receptor (see abstract).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

PATENT EXAMINER
Gerald G. Leffers Jr.
A.U. 1636